

# The antimicrobial resistance crisis? What is it and what can we do about it?

R.P. (Bob) Rennie

Professor Emeritus

University of Alberta, Faculty of Medicine and Dentistry

Edmonton, Alberta

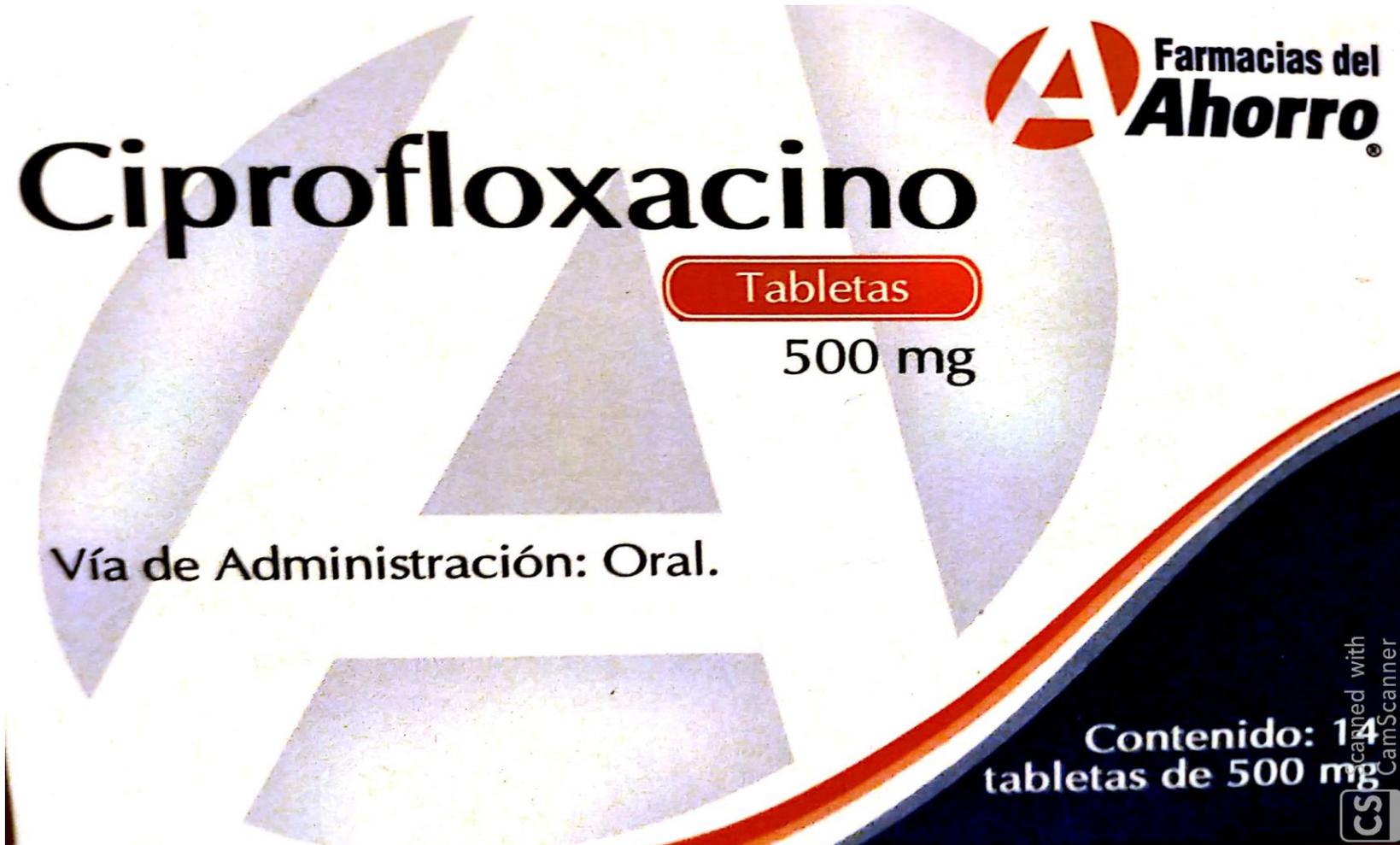
Michael. Mulvey

**Chief, Antimicrobial Resistance and Nosocomial Infections,**

**National Microbiology Lab, Public Health Agency of Canada**

**Associate Professor, Department of Medical Microbiology, University  
of Manitoba**

And they asked me if I wanted 3 packs of 14 pills (21 days of oral BID medication)!!!



# How did we get to this “crisis” – many factors

- Clinical side.
  - Most of the pressure for use of antimicrobials comes from the community
  - By “tonnage, Keflex is by far the most used antimicrobial agent in North America (probably globally) but many others are overused.
  - The greatest pressure for antimicrobial usage comes from the community
  - Lack of knowledge by clinicians about what S, I, or R means.
  - Pressure from families to treat “Mom” who has an apparent UTI when all she needs is re-hydration.
  - Lack of education for physicians.
  - Pressure from many sides to “do something”
    - We said we could do the surveillance but it was a waste of money unless more people were hired to keep the hospital clean – the answer was to outsource the cleaning to a private company to save money. The outcome was more money spent on surveillance without concomitant benefit to patient wellness (from my own experience)

# Let's look at it from the bug's perspective.

- These are the same organisms that were susceptible until we got messing with them – unwise use, pouring antibiotics into the environment, veterinary overuse, etc.
- They are just trying to survive in a hostile environment – AND – they're a lot smarter than we are!
- That doesn't mean they're more virulent but they now have a leg up (e.g. the AMR Acinetobacter from the Gulf Wars – stop transmission and they go away).
- They generally attack those who have compromising infections – and contribute to their morbidity and mortality.

# A word about “The Media”

- Up front – I hate the word “superbug”

## **Reported in the National Post within the past two weeks:**

An expert panel cautions in “When Antibiotics Fail: The growing cost of antimicrobial resistance in Canada” that the percentage of bacterial infections that are resistant to treatment is likely to grow from 26 per cent in 2018 to 40 per cent by 2050. This increase is expected to cost Canada 396,000 lives, \$120 billion in hospital expenses and \$388 billion in gross domestic product over the next three decades. This report also included the SARS outbreak, and the medical tourism cross infection in a Canadian hospital - hasn't occurred since.

## **CDC Newsroom Report Nov 13, 2019:**

- Since then (2013), the new report shows, prevention efforts have reduced deaths from antibiotic-resistant infections by 18 percent overall and by nearly 30 percent in hospitals.

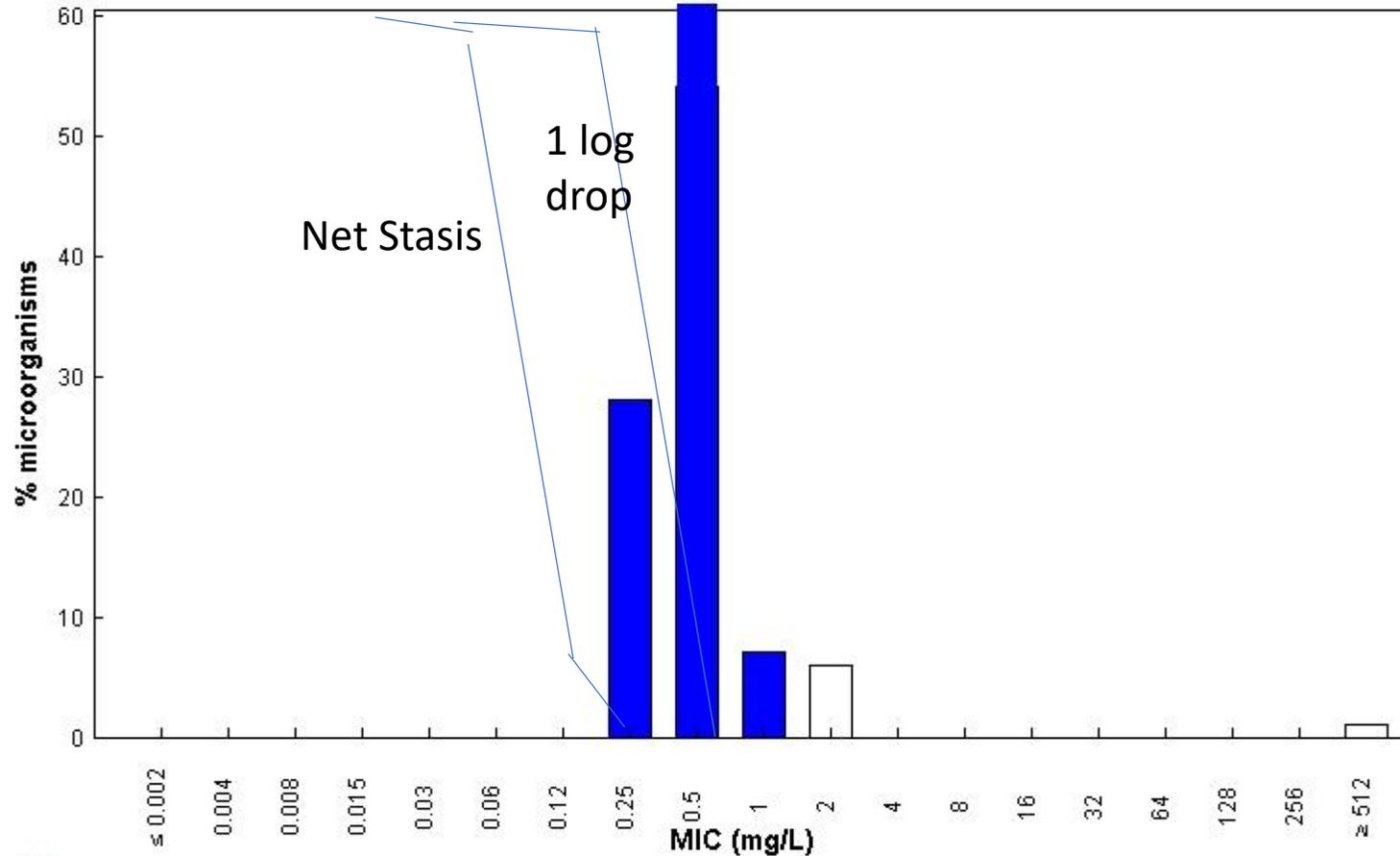
# A clinical example: ciprofloxacin and beta-haemolytic streptococci – the importance of accurate testing and reporting – and education!

- Middle-aged female patient with extensive cellulitis in the thigh that required fasciotomy and debridement. Primary treatment with intravenous penicillin. Not thought to be necrotizing fasciitis.
- Infection caused by *Streptococcus pyogenes*.
- Discussion about sending patient home on oral ciprofloxacin.
- FDA breakpoints are  $\leq 1$  – S; 2 – I,  $\geq 4$  – R.

# Target attainment for ciprofloxacin and *S. pyogenes*: 400 mg q12h IV – Net stasis and 1 log CFU decline

Ciprofloxacin / *Streptococcus pyogenes*  
International MIC Distribution - Reference Database 2016-05-23

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC  
Epidemiological cut-off (ECOFF): 1 mg/L  
Wildtype (WT) organisms: ≤ 1 mg/L

12879 observations (14 data sources)

## Ciprofloxacin and *S. pyogenes*.

- Antimicrobial susceptibility performed to determine MIC.
  - 0.5 mg/L by gradient diffusion endpoint.
- At MIC of 0.5 mg/L modeling (animal studies, Monte Carlo simulations, target attainment), shows that virtually no drug available at 0.5 mg/L even using one log decline in CFU.
- Treatment with ciprofloxacin (IV or oral will be ineffective)
- Outcome:
  - Patient remained in hospital on Penicillin and Clindamycin until resolution of infection.
  - CLSI, EUCAST, USCAST have no breakpoints for ciprofloxacin and *S. pyogenes*.
  - FDA, TPD are reviewing all the fluoroquinolones for revision of breakpoints.

# Working with clinicians.

- Antibiotic stewardship
  - Not just in the hospital but also in the community

Rennie, Weiss and Pasay – CMPT Connections. Vol 21 No. 4 Winter 2018.

- A quality initiative in a rural setting. Simple, inexpensive and effective.
- Working with local physicians to reduce antimicrobial use in urinary tract “infections”
- Pre-data gathered over three years – cultures sent to city – ID/Sens returned in 3-4 days on average.
- Switched to chromogenic agar. Produced colony count and presumptive ID by next day and reported. Provided local antibiogram to physicians.
- Three years later. Cultures reduced by 40%, Urinary tract agents collectively reduced (using DDDs) by 40%. No evidence of increased antimicrobial resistance (although numbers small). No evidence from physicians of increased morbidity or mortality.
- Burden of antimicrobials in that environment must be reduced.

# Need to better understand what susceptibility testing means

- Lab.
  - Standardized protocols.
    - ISO 20776-1:2019. Revision of Broth microdilution performance document (published).
    - ISO 2077-3. Disc Diffusion document (in preparation)\_
  - Knowledge of what is being reported.
    - What does the intermediate category mean (if anything – it changes like the wind.
    - New EUCAST version suggest Susceptible – increased dosing required.
    - In some cases (e.g. Temocillin they have made S = 0.000001mg/L and I very broad up to a resistance BKPT.
    - Labs need to temper what is thought to be “wild type” with what other parameters (PK/PD and target attainment) indicate about probable efficacy..
    - Clinicians, especially those in the community, are at sea.

# The importance of global harmonization.

- Same in vitro laboratory testing methodologies. International and ISO based).
- Clear definitions of wild-type strains and species.
- Clear definitions of susceptible, intermediate and resistant.
- Using all the parameters necessary to define a susceptible strain (It's the MIC s----!, PK, PD, target attainment, dosing, mechanisms of resistance, phenotype, etc.
- Not setting a breakpoint when it is meaningless (e.g. target cuts the “wild-type” population) or setting a breakpoint where it is important for patient care even if it means cutting the “wild type”
- Provision of a standard base to define and conduct antimicrobial resistance surveillance (singing from the same song book!).
- Establishing a collection of National Antibiotic Committees (NACs) to ensure that these tenets are practiced in each country and globally

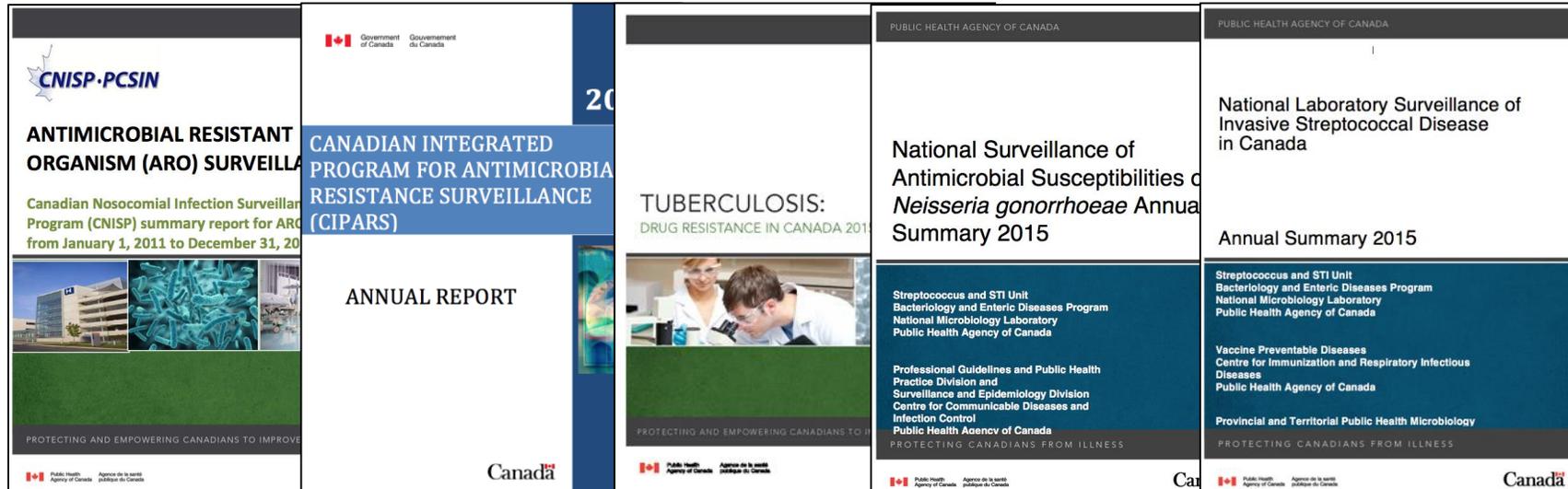
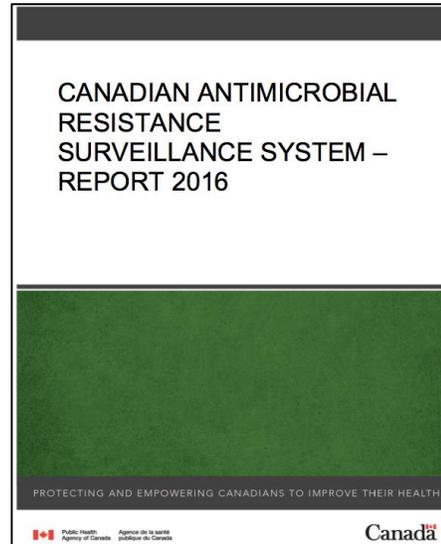
But we also need to know where these organisms are.  
Let's look at some of the great work Dr. Michael Mulvey and his colleagues at NML in Winnipeg are doing to tackle this part of the issue!

# New Developments in AMR Surveillance in Canada

## Overview

- AMRNet: A new surveillance system in Canada
- Gram Negative MDRO/XDRO Definitions in Canada
- The revolution of Whole Genome Sequencing

# PHAC Reports on AMR



# AMR Surveillance Gaps

- Community-associated AMR surveillance
- Focused studies on marginalized populations
- Improved surveillance in smaller hospitals, nursing homes, and northern communities
- Better understanding of imported AMR (human travel and imported foods)
- International Reporting



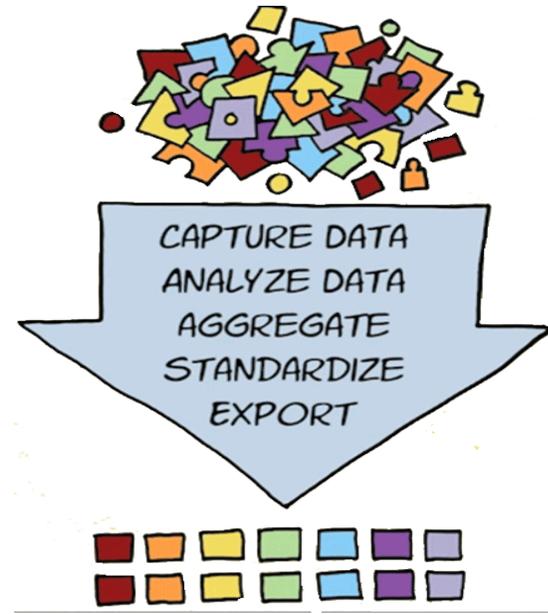
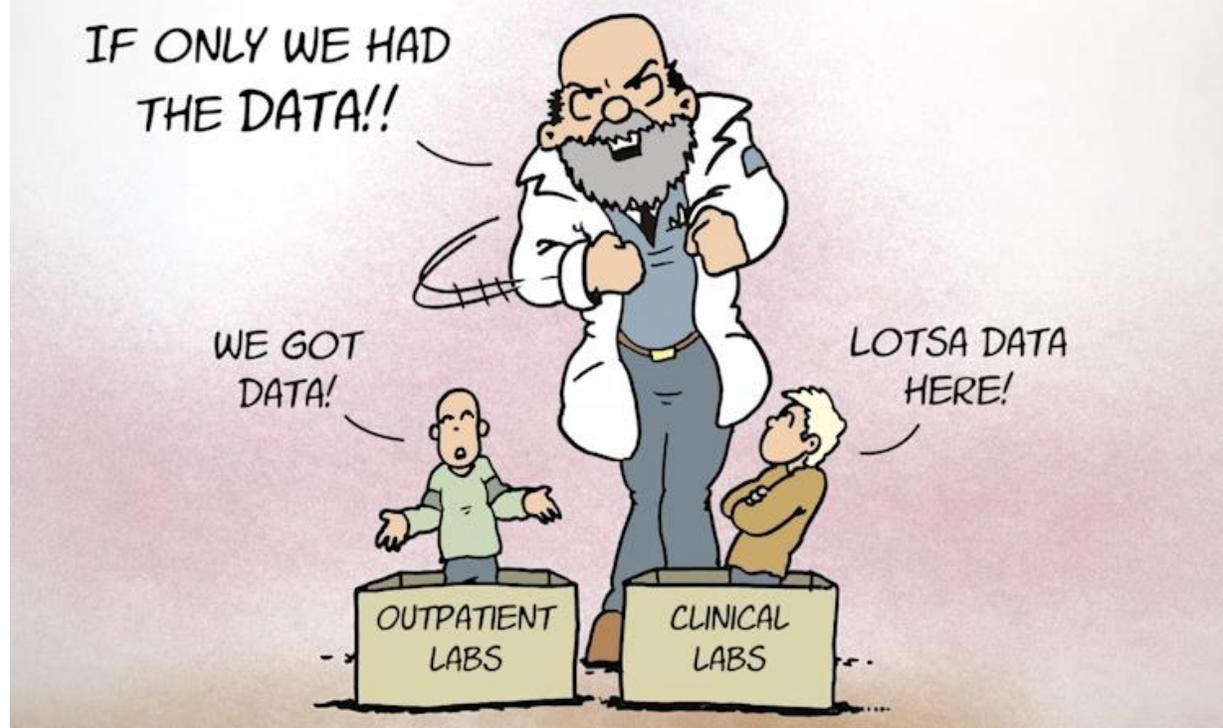
# AMR Net



**“Big data solutions to address our AMR surveillance gaps”**

# Minimum Data Requirements for AMRNet

- **Unique laboratory identification number:**
  - Anonymized, line-listed data are requested where each record represents a single bacterial isolate
- **Patient's age**
  - grouped into 5-year age categories with the exception of 0-12 months and  $\geq 90$  years.
- **Gender**
- **3 digit FSA code of the patients' address or health region**
- **Anatomical site of culture (source):**
  - eg. blood, stool, urine, skin/soft tissue, respiratory
- **Date of specimen collection (or date of isolation)**
- **In-patient and out-patient information**
- **Bacterial genus and species**
- **Antibiotic susceptibility results SIR**
  - MIC if available



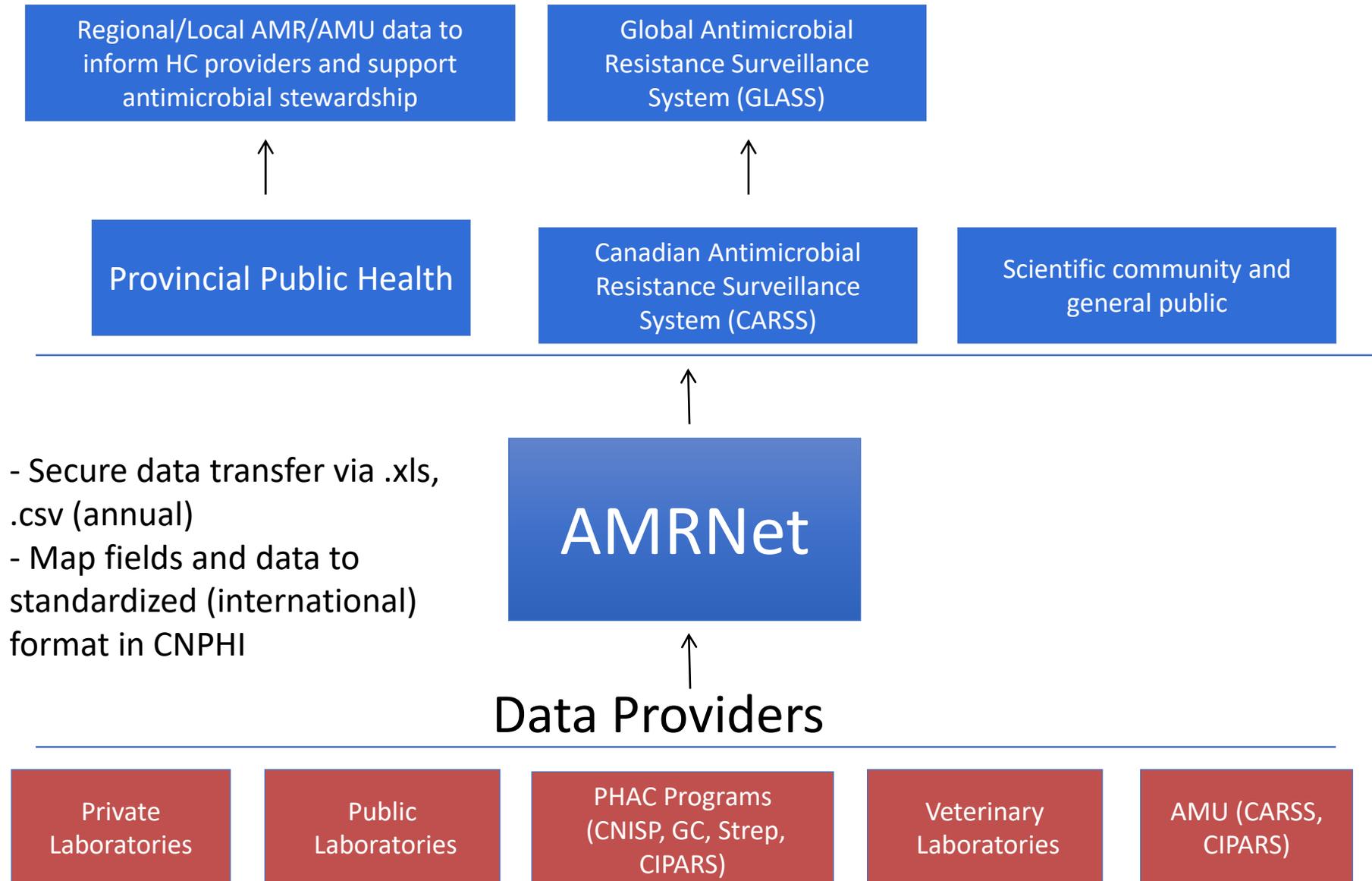
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# Challenges/Limitations

- Clinical microbiology labs:
  - Differ in algorithms and methodologies used to test bacterial isolates
  - Different antimicrobial panels
  - Operate different lab information systems and the data fields are not standardized
  - Different reporting algorithms – Clinical lab data vs physician reporting
- Other considerations:
  - Duplicate isolates
  - In-patient vs out-patient data (LTC, nursing homes, community)
  - Data sharing agreements/privacy issues
  - Data interpretation standards and validation (SIR)

# Proposed Data Flow for AMRNet



# Where are we now with AMRNet?

- Agreements with provinces to initiate data collection network
  - Ontario, BC, Sask, NF, and PEI
  - Currently discussions with DynaCare and LifeLabs
  - Scoping out other provinces completed
- Working with Privacy Management Division to ensure privacy issues met
- Developing data sharing agreements BC, Ont, PEI, Sask, NS
- Reaching out to veterinary clinical labs and associations for input
- Federal Data
  - *C. difficile* data approved by CNISP
  - GC and Salmonella (CIPARS) data in consultation

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# Who is the Canadian Public Health Laboratory Network AMR Working Group?

- Microbiology Labs from each province which also includes:
  - All 11 public health microbiology laboratories including the NML
  - Three large private laboratories now encompassing all of private testing in BC and Ontario.
  - Six members of the group also serve at acute care laboratories
  - AB, MB, QC, NB, PE, NS
  - Five members of the group are also Inf. Dis. Physicians / Consultants
  - MB, QC, NB, PE, NS.



**Recommandations provisoires concernant la déclaration des isolats ultrarésistants et panrésistants de la famille des Enterobacteriaceae, de Pseudomonas aeruginosa, du genre Acinetobacter spp. et de Stenotrophomonas maltophilia**

German GJ<sup>1</sup>, Jamieson FB<sup>2</sup>, Gilmour M<sup>3</sup>, Almohri H<sup>4</sup>, Bullard J<sup>5</sup>, Domingo MC<sup>6</sup>, Fuller J<sup>7</sup>, Girouard G<sup>8</sup>, Haldane D<sup>9</sup>, Hoang L<sup>10</sup>, Levett PN<sup>11</sup>, Longtin J<sup>6</sup>, Melano R<sup>2</sup>, Needle R<sup>12</sup>, Patel SN<sup>2</sup>, Rebbapragada A<sup>13</sup>, Reyes RC<sup>14</sup>, and Mulvey MR<sup>3\*</sup>

**Interim recommendations for the reporting of extensively drug resistant and pan-drug resistant isolates of Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia**

German GJ<sup>1</sup>, Jamieson FB<sup>2</sup>, Gilmour M<sup>3</sup>, Almohri H<sup>4</sup>, Bullard J<sup>5</sup>, Domingo MC<sup>6</sup>, Fuller J<sup>7</sup>, Girouard G<sup>8</sup>, Haldane D<sup>9</sup>, Hoang L<sup>10</sup>, Levett PN<sup>11</sup>, Longtin J<sup>6</sup>, Melano R<sup>2</sup>, Needle R<sup>12</sup>, Patel SN<sup>2</sup>, Rebbapragada A<sup>13</sup>, Reyes RC<sup>14</sup>, and Mulvey MR<sup>3\*</sup>

# Distribution of Guidelines

- Distributed Recommendations to all laboratories and AMR working groups in provinces
- Distributed to national and International groups
- Received over 11 pages of comments
  - Many positive comments
  - Algorithms complicated to implement
  - Potentially Cost prohibitive for some labs
  - Public Health (Reportable) and Infection Control Implications (Precautions)
  - Concerns if the data would be useful to collect
  - Concerns of organisms (Steno) and CF Infections



## ADVISORY COMMITTEE STATEMENT

# Canadian recommendations for laboratory interpretation of multiple or extensive drug resistance in clinical isolates of *Enterobacteriaceae*, *Acinetobacter* species and *Pseudomonas aeruginosa*

GJ German<sup>1</sup>, M Gilmour<sup>2</sup>, G Tipples<sup>3</sup>, HJ Adam<sup>4</sup>, H Almohri<sup>5</sup>, J Bullard<sup>6</sup>, T Dingle<sup>3</sup>, D Farrell<sup>7</sup>, G Girouard<sup>8</sup>, D Haldane<sup>9</sup>, L Hoang<sup>10</sup>, PN Levett<sup>7</sup>, R Melano<sup>11</sup>, J Minion<sup>12</sup>, R Needle<sup>13</sup>, SN Patel<sup>11</sup>, R Rennie<sup>3</sup>, RC Reyes<sup>14</sup>, J Longtin<sup>15</sup>, MR Mulvey<sup>2\*</sup>

Canadian Communicable Disease Reports. 2018. Vol 14:29-34.

**Table 2: Definitions for the determination of MDRO/XDRO in select organisms**

MDRO		XDRO	
Definition	Antimicrobial groups	Definition	Antimicrobial groups
Enterobacteriaceae			
Resistance to THREE OR FOUR of the SIX antimicrobial groups	Tobramycin OR <sup>a</sup> gentamicin <sup>b</sup>	Resistance to FIVE OR SIX of the antimicrobial groups	Tobramycin OR gentamicin
	Piperacillin-tazobactam		Piperacillin-tazobactam
	Imipenem OR meropenem <sup>c</sup>		Imipenem OR meropenem
	Cefotaxime OR ceftriaxone OR ceftazidime		Cefotaxime OR ceftriaxone OR ceftazidime
	Ciprofloxacin		Ciprofloxacin
	Trimethoprim-sulfamethoxazole		Trimethoprim-sulfamethoxazole
Organisms: <i>Pseudomonas aeruginosa</i> OR <i>Acinetobacter</i> species			
Not applicable	Not applicable	Resistance to ALL FIVE antimicrobial groups	Ciprofloxacin
			Piperacillin-tazobactam <sup>d</sup>
			Ceftazidime
			Imipenem OR meropenem
			Tobramycin

Abbreviations: MDRO, multidrug resistant organisms; XDRO, extensively drug resistant organisms

<sup>a</sup> The term 'OR' should be interpreted as follows: if an isolate is resistant to either antimicrobial agent listed, it should be considered resistant to that criterion for the purposes of these definitions

<sup>b</sup> Resistance in *Serratia* spp. should only consider gentamicin susceptibility testing results

<sup>c</sup> Resistance in *Proteus* spp. should only consider meropenem susceptibility testing results

<sup>d</sup> Resistance in *P. aeruginosa* may include piperacillin-tazobactam OR piperacillin. For all *Acinetobacter* spp. piperacillin-tazobactam must be used

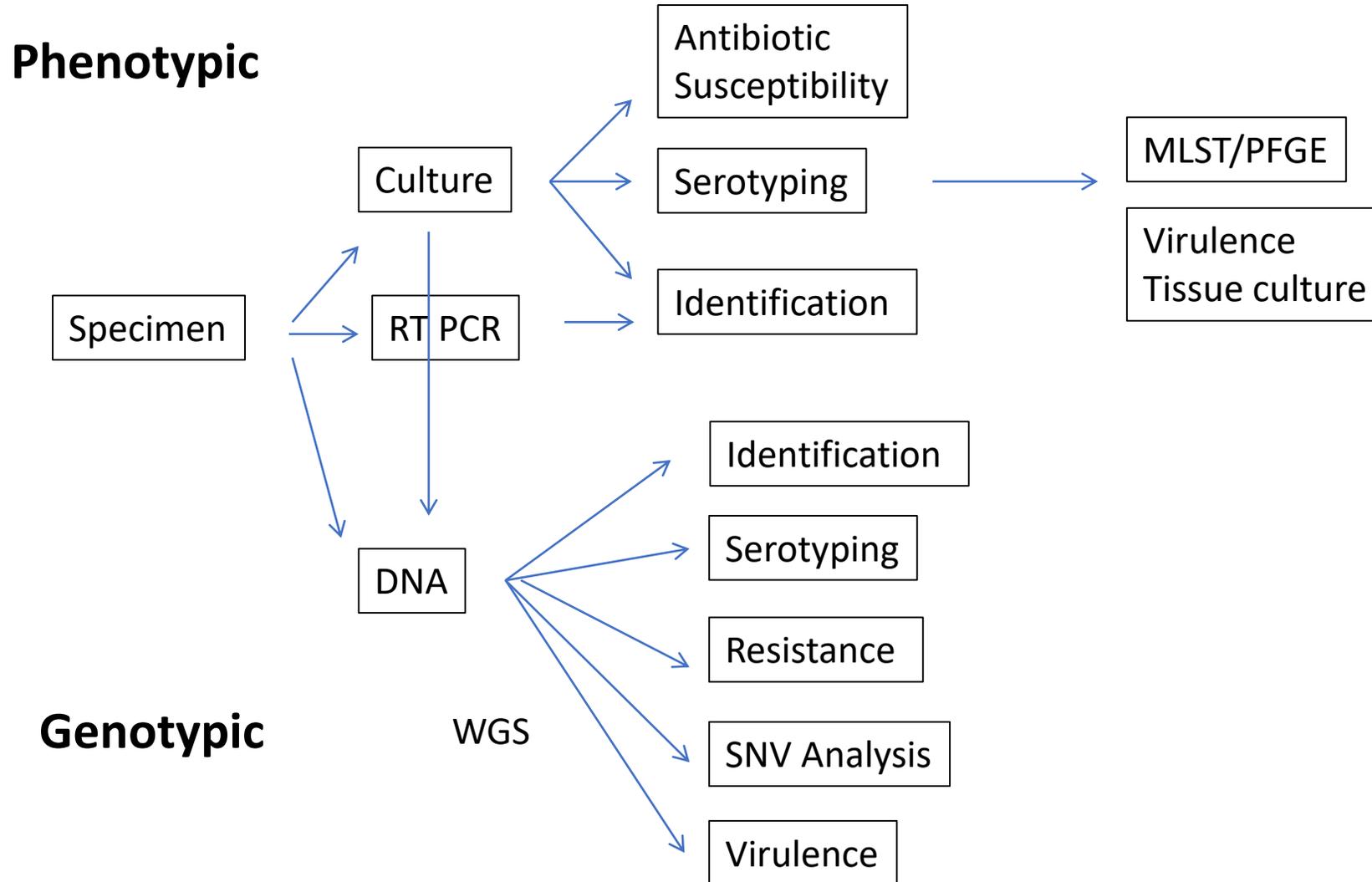
Why do we do this...

- **Surveillance**
- **Stewardship**
- **Infection Control**

# New Developments

- Working with bioMerieux
  - Developed Vitek2 algorithms for predicting MDRO/XDRO for Enterobacteriales, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.
  - Tested algorithms *in silico*
  - CANWARD Program isolates selected for MDRO/XDRO panel for distribution for wet lab validation
  - WGS performed on all test isolates
- Contacting other companies to develop algorithms
- AMRNet developing algorithms to report MDRO/XDRO
- Exploration into reporting into Canadian Notifiable Disease Surveillance System

# WGS Revolution in the Clinical Setting

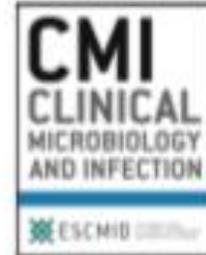




Contents lists available at ScienceDirect

## Clinical Microbiology and Infection

journal homepage: [www.clinicalmicrobiologyandinfection.com](http://www.clinicalmicrobiologyandinfection.com)

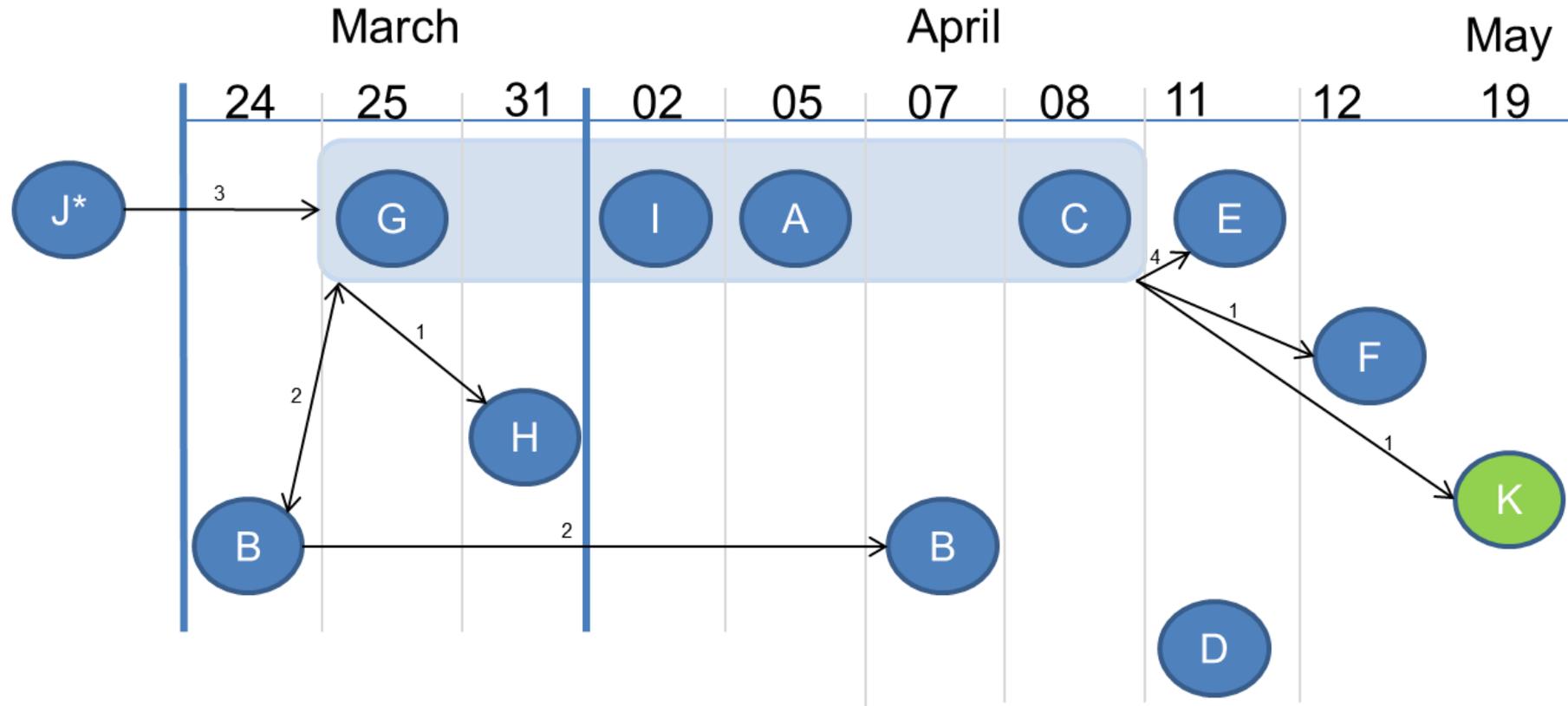


### Review

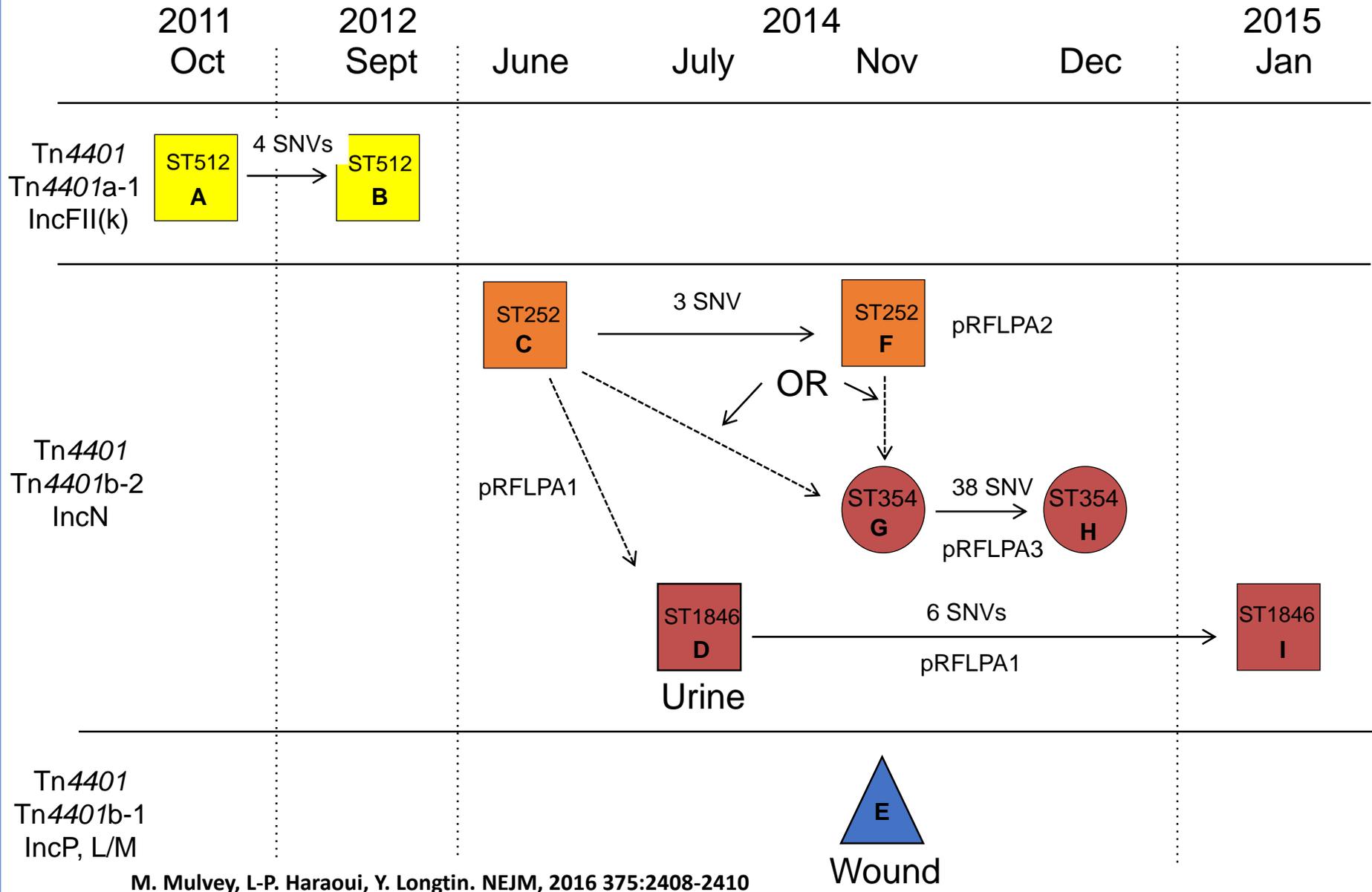
## The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee

M.J. Ellington<sup>1,†</sup>, O. Ekelund<sup>2,†</sup>, F.M. Aarestrup<sup>3</sup>, R. Canton<sup>4</sup>, M. Doumith<sup>1</sup>, C. Giske<sup>5</sup>, H. Grundman<sup>6</sup>, H. Hasman<sup>7</sup>, M.T.G. Holden<sup>8</sup>, K.L. Hopkins<sup>1</sup>, J. Iredell<sup>9</sup>, G. Kahlmeter<sup>2</sup>, C.U. Köser<sup>10</sup>, A. MacGowan<sup>11</sup>, D. Mevius<sup>12,13</sup>, M. Mulvey<sup>14</sup>, T. Naas<sup>15</sup>, T. Peto<sup>16</sup>, J.-M. Rolain<sup>17</sup>, Ø. Samuelsen<sup>18</sup>, N. Woodford<sup>1,\*</sup>

# Potential Mode of transmission



# Super carrier of KPC carbapenemase



# Summary

- WGS revolutionizing the way we characterize isolates
- Many surveillance programs moving to WGS
- More research in AMR prediction required for many organisms

# What conclusions can we make?

- The problem requires a multifaceted approach.
  - Education of the public and physicians about the overuse of antimicrobial agents.
  - Standardization of antimicrobial susceptibility testing so we are all testing and reporting in the same manner
  - Ensuring that the testing systems we use are fit for use with new breakpoints, and reporting parameters. We keep hearing that it takes 4-5 years for AST manufacturers to change their panels. Government (e.g. FDA and other regulators) need to streamline that process (e.g. revisions to ISO 20776-2 are underway to hopefully facilitate that process)
  - Antimicrobial stewardship – where it has the biggest bang for the buck
  - Surveillance that makes sense – that provides us with another tool to drive the message.

# The end result is – hopefully

- Better patient management,
- Lower “attributable” morbidity and mortality
- Appropriate and factual social media – good news doesn’t sell as well as gloom and doom.
- Ability of new agents – used wisely – to control the spread of infectious agents.